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THE PHYSICAL BASIS OF LIFE

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THE FIRST
WILLIAM THOMPSON SEDGWICK
MEMORIAL LECTURE

DELIVERED IN HUNTINGTON HALL,
BOSTON, MASSACHUSETTS, DECEMBER 29, 1922

FOR the purpose of commemorating the services of William Thompson Sedgwick to the cause of Biology and Public Health there has been established a Memorial Lectureship in the department of the Massachusetts Institute of Technology which he created. The desire of the founders is that the Sedgwick Memorial Lectures shall be given from year to year by men of distinguished eminence in any one of the subjects comprehended within the general scope of Biology and Public Health in order that it may fittingly express the deep and broad sympathy of the man whom the Lectureship is designed to honor.

THE PHYSICAL BASIS OF LIFE

BY

EDMUND B. WILSON

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THE PHYSICAL BASIS OF LIFE*

I HAVE been much honored by the invitation to speak on this occasion, but for me it has meant more; for the man in whose memory the Sedgwick Memorial Lectureship has been established was my lifelong and cherished friend. My theme today is drawn from an infinitesimal but all-including world, bounded by the horizon of the compound microscope, a world that may seem far distant from Sedgwick's own broad domain of sanitary science and the public health. I am sure, however, that such would not have been his own view; for Sedgwick was one of the pioneer teachers of general biology in this country, and it was his lifelong habit to think of the phenomena of life in terms of the activities of protoplasm.

I have a lively recollection of how he and I, in the days of our youth, when fellow students at Yale, fell under the spell of Huxley's Edinburgh address on the *Physical Basis of Life*,[1] at that time still a subject of widespread popular discussion. In this celebrated discourse the eminent English biologist set forth certain general conclusions concerning protoplasm which had gradually taken shape through the work of such investigators as De Bary, Max Schultze, Kühne, Brücke and Lionel Beale. Huxley's presentation of the subject was a masterpiece both of English style and of philosophical breadth of outlook. In part for this reason, still more because of its sup-

*A few references to the literature, indicated by numerals in the text, will be found at the end.

posedly materialistic implications, it aroused immediate and widespread public attention. Huxley himself warned that to accept his conclusions would be to place one's foot on the first rung of a ladder which in most people's estimation is the reverse of Jacob's and leads to the antipodes of heaven; nevertheless, he insisted that he was individually no materialist but on the contrary believed materialism to involve grave philosophic error. Despite this disclaimer, his conclusions aroused a storm of criticism and protest which came to a climax a few years later when Tyndall, in the famous Belfast address, proclaimed his faith in non-living matter as offering the "promise and potency of all terrestrial life."[2]

It is not surprising that such pronouncements should have had a hostile reception fifty years ago. Even in this twentieth century some of our non-scientific friends somehow manage to find a source of heat and fury in so evident a fact as organic evolution. On the whole, however, sane and well-informed persons do not now seem to find either their morals or their happiness seriously affected by elementary and fundamental facts concerning living things. Today Huxley's heresy of sixty years ago has become an orthodox platitude; but the problems of protoplasm still hold us fast with a gripping interest that has lost nothing of its force with the flight of time. In what light do Huxley's conclusions appear after the biological progress of half a century?

It is necessary to bear in mind that those conclusions were formulated before modern cytology had been born, and long before the cell had been clearly thought of as a colloidal system. From our present point of view we employ the word protoplasm as a collective term to designate the substances that constitute the active or living materials of which cells are composed. I use the plural form,

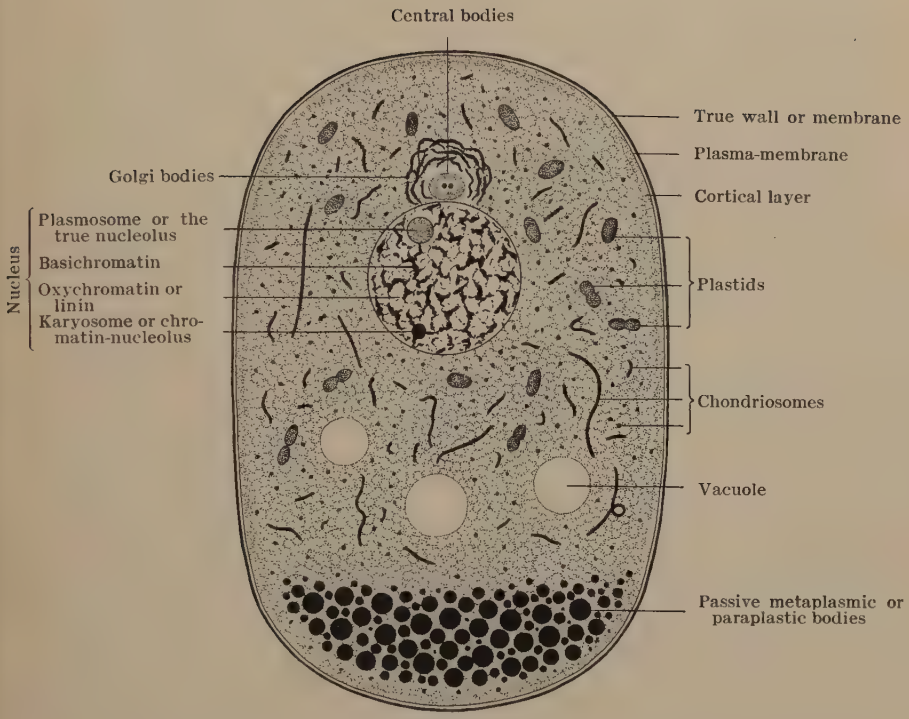

FIG. 1

Generalized diagram of an animal cell, to show some of its more important formed components.

substances, advisedly; for it is here in the first place, that Huxley's statements now require recasting in more modern terms. To many readers his discussion conveyed the impression that protoplasm is a single chemical substance or "living protein." In his opening words he spoke of the physical basis of life as "some one kind of matter common to all living beings." He pictured a union of lifeless substances, such as water, ammonia and carbon dioxide, to form "the still more complex body, protoplasm"; and the properties of this substance, he affirmed, must result from the nature and disposition of its molecules. "The thoughts to which I am now giving utterance," said Huxley, "and your thoughts regarding them, are the expression of molecular changes in that matter of life which is the source of our other vital phenomena."

In a broad sense these words are true; but evidently they do not express the whole truth. Long ago it became perfectly clear that what we call protoplasm is not chemically a single, homogeneous substance. It is a mixture of many substances, a mixture in high degree complex and the seat of varied and incessant chemical transformations, yet one which somehow holds fast for countless generations to its own specific type. How, in view of all this, can we speak of a molecule of protoplasm? We might indeed suppose—it actually has been supposed—that protoplasm consists of very large molecules (plastidules, micellae or biogens) into which all these various substances, or their components, may be built; but even were such an hypothesis tenable it would leave out of account precisely that which to many investigators seems the most fundamental part of the problem. The evidence from every source demonstrates that the cell is a complex organism, a microcosm, a *living system.* With the microscope we distinguish in this system (Fig. 1)[3] a clear and appar-

ently structureless ground-substance or *hyaloplasm* in which are suspended a great variety of visibly different formed bodies, widely diverse in form and function, each of which plays its own particular part in the activities of the system. Examples of these bodies are, first of all, the nucleus, and then the cytoplasmic chondriosomes and plastids, the Golgi-bodies and central bodies and many kinds of granules and fibrillae. The functions of these various bodies are still imperfectly known; but all, undoubtedly, are centers of specific chemical activities which contribute in one way or another to the life of the system. This fact is perhaps most clearly evident in case of the plastids, especially characteristic of the cells of plants, which are obviously specific centers for the formation of starch, chlorophyll and other pigments, and apparently also in some cases of fats and proteins. The nucleus plays an important part in growth and other constructive processes; it is possibly a center for the production of enzymes; and it is of fundamental importance, though not the sole factor, in heredity. The central bodies operate primarily as foci of cell-division; sometimes as organs for the production of cilia or flagella; and under certain conditions as centers of aggregation for other formed bodies. The granules often represent local accumulation of storage-products of many kinds, such as food materials, excretory products, pigment, pro-enzymes or the like and a great variety of others; but, taken as a whole, the granules may have a much broader significance than this would seem to imply. The varied functions of the fibrillae include contractility, conduction of stimuli, and the support of the softer cell-structures; they also often seem to play an important part in the processes of secretion. The significance of the chondriosomes is not yet definitely known. An important group of observers have

held that it is by the transformation of these bodies that many of the other formed bodies of the cell arise, including the plastids, and various forms of granules and fibrillae; but the correctness of this view is still far short of demonstration.[4] The Golgi-bodies are of still more doubtful significance. They are known to play a definite part in the formation of the sperm-cells, and evidence is beginning to accumulate that they may be concerned in the processes of secretion; but we may feel sure that these bodies are of far greater importance than this meager list indicates, for they seem to be almost omnipresent in the cells of animals and will probably be found as generally in plant-cells.

Some of these formed bodies seem to be permanent, others to be transitory formations that come and go in the kaleidoscopic operations of cell-life. Which of them are alive? Which of them, if any, constitute the physical basis of life? What, in other words, is protoplasm?

These are embarrassing questions. One of the most pleasing functions of the teacher of elementary biology is to demonstrate to the laboratory student the substance of a living cell, assuring him cheerfully that he is beholding protoplasm; and by good luck it rarely occurs to the disciple to cross-examine his master on the subject. Were it otherwise how many a bad quarter of an hour might we have to endure! For the truth is that the more critically we study the question, the more evident does it become that we can not single out any one particular component of the cell as the living stuff, *par excellence*. Of this fact most experienced cytologists, including such eminent leaders as Flemming, Strasburger, Bütschli, Kölliker and Heidenhain, long since became convinced. "No man," said Flemming, "can definitely say what protoplasm is. . . . In my view that which lives is the entire body of

FIG. 2

The earlier stages or prophases of division in epithelial nuclei of the larval salamander (from HEIDENHAIN). The formation and splitting of the nuclear threads (spireme) accurately shown in A, B, and C; D, their condensation to form the chromosomes.

the cell.'"[5] It is this view of the physical basis of life that has impressed us more and more as our knowledge of the cell has advanced; and this is as true of the physiologist and the chemist as of the cytologist. I quote a distinguished biochemist. "We can not," says Professor Hopkins, "without gross misuse of terms, speak of the cell-life as being associated with any particular type of molecule. Its life is the expression of a particular dynamic equilibrium which obtains in a polyphasic system. Certain of the phases may be separated, but life is a property of the cell as a whole, because it depends upon the equilibrium displayed by the totality of co-existing phases.'"[6] This conclusion is precisely the same as that of the cytologist; for him, as has often been said, the word protoplasm stands for a morphological concept, not for a chemical one.

At present we know living systems only in the form of cells or their products; for every organism is, or at some time has been, a cell. I repeat, therefore, that when we speak of protoplasm as the physical basis of life, we mean simply the sum total of all the substances that play any active part in the cell-life; and certainly we can not limit the list to such substances as the proteins, carbohydrates or lipins. We must include a multitude of others, not excepting inorganic salts and water, which are often characterized as "lifeless." At first sight this may seem a rather barren conclusion; but the fact is quite otherwise. No conception of modern biology offers greater promise for the physico-chemical analysis of vital phenomena than that the cell is a colloidal system; and that what we call life is, in the words of Czapek, a complex of innumerable chemical reactions in the substance of this system. Modern investigation has indeed already profited so much by the point of view here offered as to suggest that

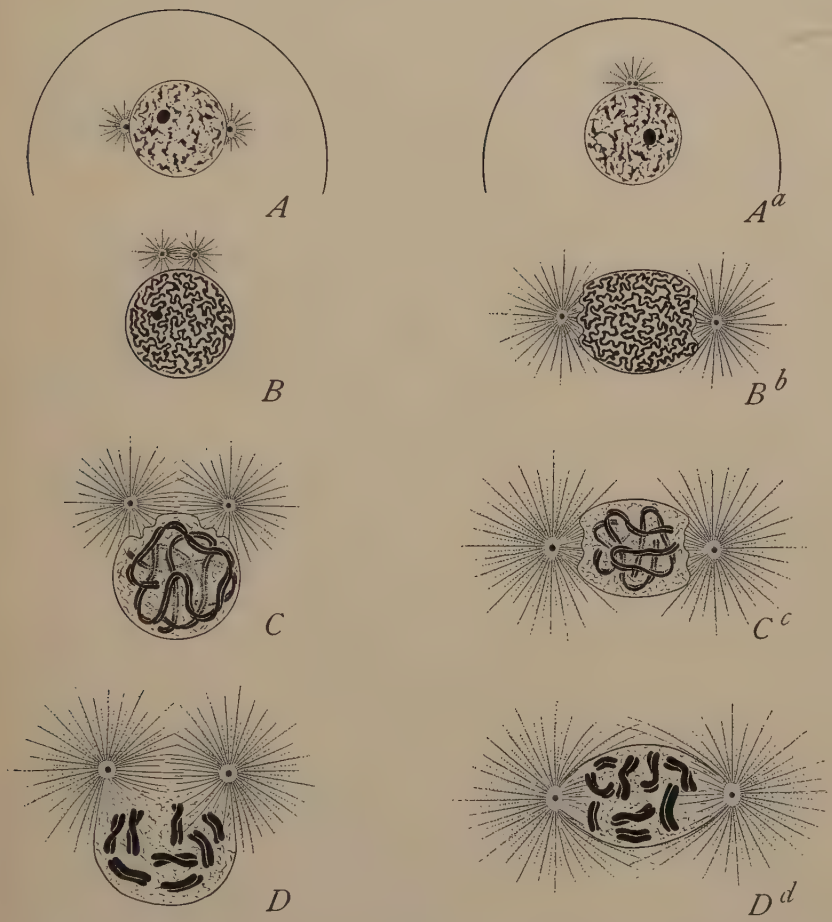

FIG. 3

Diagram of the prophases of nuclear division (mitosis), showing two somewhat different types, leading to the same result.

the study of protoplasm and the cell may be destined to pass more and more into the hands of the physiologist, the physicist and the chemist; and certainly the rising tide of cell-research in these directions is of good augury for the future experimental analysis of vital phenomena. There are, however, other aspects of the problem which for the present escape the precise quantitative methods of the physicist and chemist, or are only beginning to come within their range, but are none the less essential to our view of the general problem. I refer to those phenomena with which the cytologist, the geneticist and the embryologist must try to deal; and it is especially to the aspects of the problem which these present that I here ask attention.

The cytologist is first of all struck by the extraordinary pains that nature seems to take to ensure the perpetuation and accurate distribution of the components of the system in cell-division, and hence in heredity. Nothing is more impressive than the demonstration of this offered by the nucleus of the cell; but its obvious meaning is often disregarded or treated with a blind scepticism which pretends that no meaning exists. To our limited intelligence, it would seem a simple task to divide a nucleus into equal parts. The cell, manifestly, entertains a very different opinion. Nothing could be more unlike our expectation than the astonishing sight that is step by step unfolded to our view by the actual performance. The nucleus is cut in two in such a manner that every portion of its net-like inner structure is divided with exact equality between the two daughter-nuclei, and the cell performs this spectacular feat with an air of complete and intelligent assurance. The net-like framework is spun out into long threads or chromosomes (Figs. 2, 3); these are divided lengthwise into exactly similar halves; they shorten, thicken, sepa-

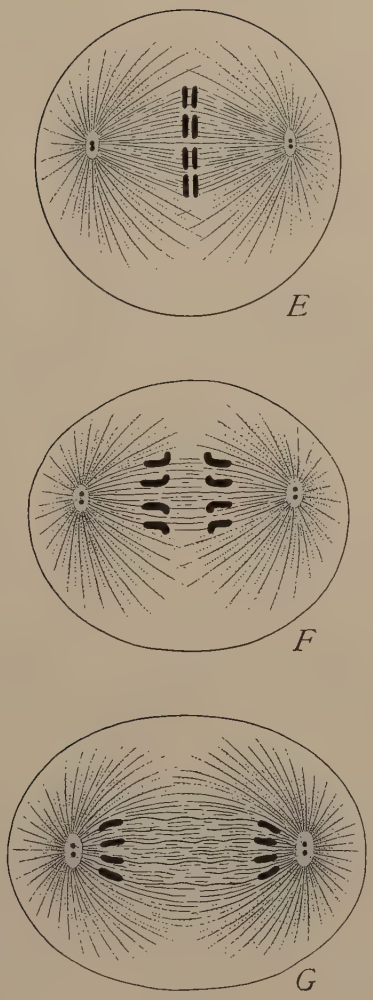

FIG. 4

Diagram of the middle stages of cell-division common to both the types shown in Fig. 3.

rate and pass to opposite poles (Fig. 4); and from the two groups formed, are built up two daughter-nuclei, while the cell-body divides between them (Fig. 5). Such a process seems in some respects to contradict all physical principles; but its meaning has now become perfectly plain. In a general way it means, as Roux pointed out forty years ago, that the nucleus is not composed of a single homogeneous substance, but is made up of different and self-perpetuating components; and it means that these components are strung out in linear alignment in the threads so that they may be divided, or distributed in particular manner, by doubling of the thread.[7]

This remarkable conclusion led the way in a series of investigations that have brought forth some of the most notable discoveries of our time. Roux's theoretical conclusion was preceded and perhaps suggested by earlier cytological observations which indicated that the nuclear threads contain smaller bodies suspended in a clear basis and aligned in a single, regular series. The further conclusion was thus suggested that the longitudinal splitting of the thread might be due to fission of these bodies. Later cytological observations confirmed and considerably extended these conclusions, showing that in some cases the smaller bodies or "chromomeres" aligned within the nuclear threads are of different sizes and show a constant serial order.[8] Thus far, cytologists have been able to demonstrate these facts in only a rather fragmentary and general fashion (Fig. 6); and it seems certain that the visible structure of the threads (only to be seen in sections of fixed or coagulated material) is no more than a rough expression of a finer structure lying beyond the present reach of the microscope. Here, however, genetic research has come to the rescue, bringing forward indirect proof on a grand scale derived from experiments

on the mechanism of Mendelian heredity. These experiments, due especially to Morgan, Sturtevant, Bridges and a large group of their co-workers, have accumulated and thoroughly analyzed a great body of accurate data in a series of works that have almost revolutionized the study of heredity.[9]

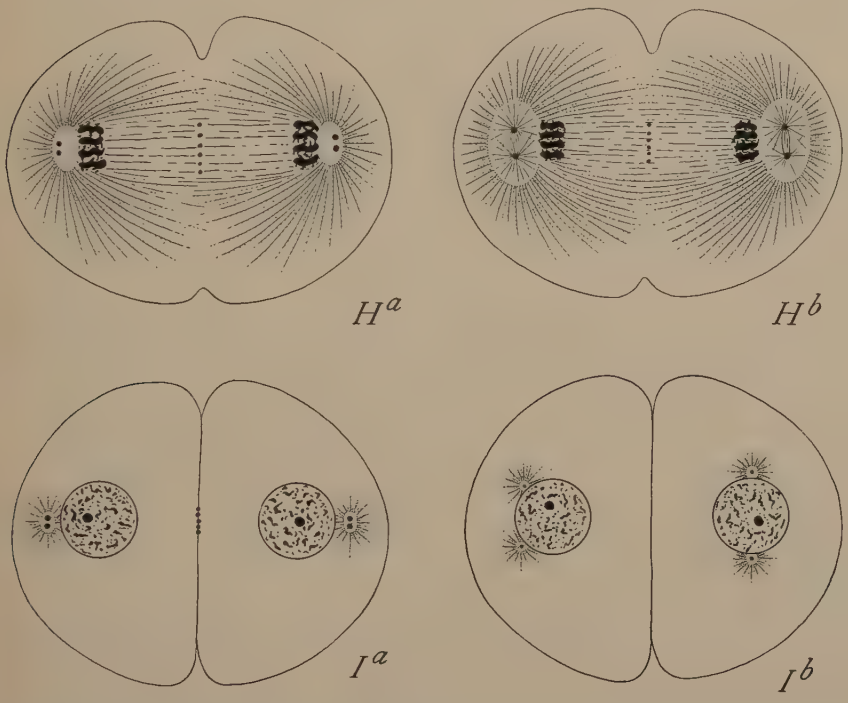

FIG. 5

Diagram of the closing phases of cell-division, showing final stages of the two types shown in Fig. 3.

I regret the necessity that limits my account of these researches, and of what led up to them, to a bare indication of their most general results. They have, in the first place, finally demonstrated the fact, indicated in a more general way by earlier observers, that the nuclear threads or chromosomes stand among the primary factors of hered-

ity. The pioneer investigations of Hertwig, Strasburger, Van Beneden and Boveri long since produced strong evidence that the nucleus of the cell has an especial significance in the operations of heredity. Sutton had shown that the more obvious of the Mendelian phenomena, at first sight seemingly so inscrutable, find a simple and intelligible explanation in the combinations, segregations and recombinations of the chromosomes. De Vries, Correns and Strasburger had urged the importance from the genetic point of view of Roux's conception of the chromosomes as representing linear series of smaller bodies that are somehow concerned with the determination of particular hereditary characters; but these writers made no approach to an adequate interpretation of the phenomena, even as then known.[10] The subject first began to take on more definite form with the initial experimental investigations of Morgan and of Sturtevant, which brought very strong support to the conception of the chromosomes as linear aggregates, showing in particular that this conception affords a complete explanation of the genetic phenomena known as linkage and recombination by "crossing-over." For all this the way had in some degree been prepared by earlier investigations; but the further conclusions which soon followed seemed at first sight completely incredible. Step by step the experimental analysis built up the demonstration that the infinitesimal entities serially aligned in the nuclear threads are primary and indivisible units or factors of heredity ("genes"), each of its own specific kind and self-perpetuating by growth and division; that they are of definite number; that they are separated by fairly definite and constant intervals; and that in their serial alignment *they follow a definite and invariable order!* When we try to reckon with this series of conclusions, we find ourselves fairly gasping for

breath. Such results are indeed staggering—to a certain type of mind even harder to assimilate than those which physicists are now asking us to accept concerning the structure of atoms. *Nevertheless they are probably true!*

Let me emphasize the fact that these conclusions are not a product of the seventeenth century but of the twentieth. They did not arise in the fertile imagination of

FIG. 6

Structure of the nuclear threads from oöcytes of the flat-worm *Dendrocoelum* (from GELEI). The threads are longitudinally divided and show in each case a double series of smaller bodies or chromomeres.

a Bonnet, a Buffon or a Weismann. They were the outcome of accurate and extended experiments under carefully controlled conditions; they make possible precise quantitative prediction concerning the outcome of new experiments. In these respects they are employed in the same way as the exact concepts of the chemist or the physicist and they may, I think, lay claim to a validity of the same kind even if it be not yet quite of the same degree. It is theoretically possible, I suppose, to consider

them as nothing more than a convenient fiction or algebraic symbolism, a kind of ideal mental model by means of which the genetic facts may conveniently be grouped. Those, however, who prefer to take their point of departure in the observed cytological facts will be more likely to make use of the actual model which every dividing cell displays to us invisible reality—a model that is not less impressive because at present the cytologist sees it only in broad outline with no more than dim indications of the finer complications inferred from the results of genetic research. At any rate it was this actual model that gave the point of departure for the foregoing conceptions concerning the nuclear organization and thus made possible some of the most fundamental of modern experimental researches on heredity. Considered only as working instruments, therefore, these conceptions have a practical value almost comparable to that of the atomic theory as employed in chemistry and physics.

Cytology and genetics have thus combined to make real to us the existence of a nuclear microcosm that is as complex and wonderful as any pictured by the fantasies of the speculative nature-philosophers. But manifestly we can not halt here. The nucleus is part of a larger system, the cell; and our inquiry must now enlarge its scope in order to consider the organization of that system considered as a whole. We are thus led, first of all, to the question whether an organization similar in type to that of the nucleus, or anything approaching to it, may also exist in the protoplasm of the cytosome (cytoplasm) or extranuclear region of the cell-system. Conservative cytological opinion has been extremely reluctant even to recognize such a possibility. We have been prone to take the cytoplasmic region of the cell-system at its face value, conceiving it as a vague and formless mass devoid of definite

organization, or organized only under the domination of the nucleus. We have been accustomed to think of its history in cell-division as a simple mass-division showing a fundamental contrast to the complicated meristic process seen in nuclear division. Facts are however slowly accumulating which may compel a revision of this notion. Re-

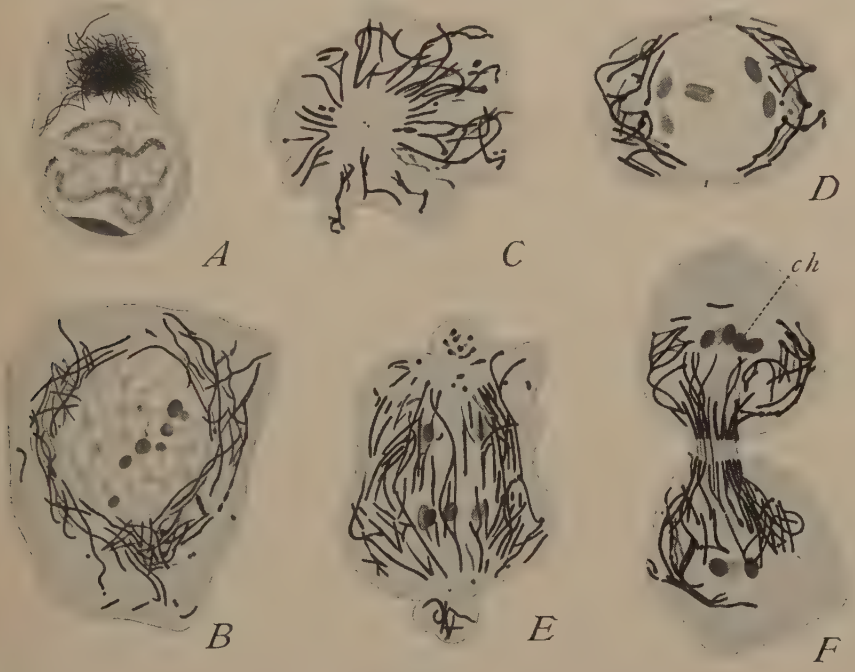

FIG. 7

Cell-division in the spermatocytes of the hemipter *Euschistus* showing the behavior of the chondriosomes (from BOWEN). These have here the form of numerous rods (black), which in F are seen separating into two groups as the cell divides.

cent cytological studies bring prominently into view the fact that many of the formed bodies are directly transmitted, either as such or in the form of pre-existing specific material, from mother-cell to daughter-cell. And there is growing evidence that this operation is not an incidental hit or miss process, as formerly supposed, but

one that is definitely ordered, even though it be not comparable in precision with that which so impresses us in case of the nuclear division.

Vague indications of such a conclusion were long since given by the plastids of plant-cells, which are certainly in

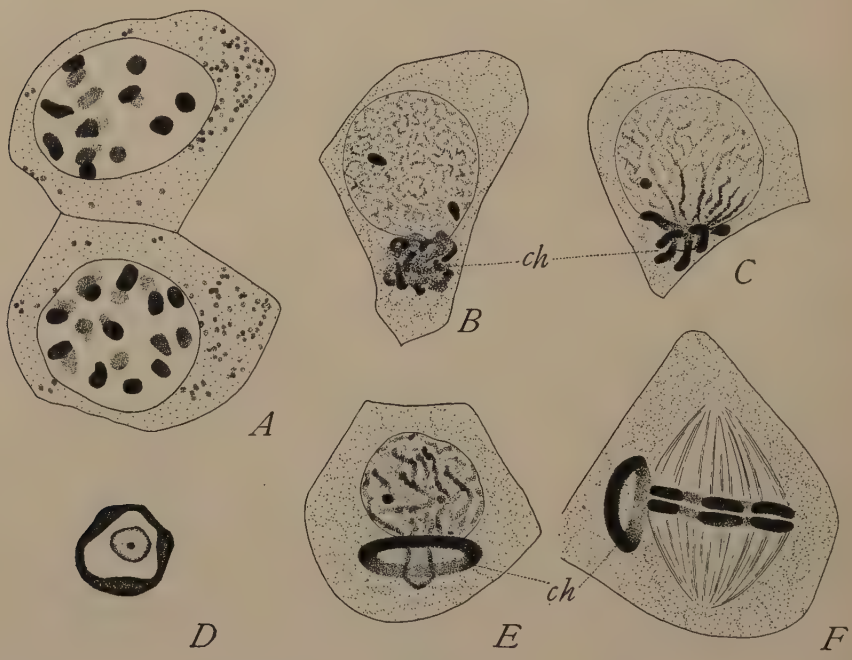

FIG. 8

Early stages of division in the spermatocytes of the scorpion *Centrurus*, showing the aggregation of minute chondriosomes (mitochondria) to form larger rod-like bodies near the nucleus (B, C), and their final aggregation to form a single ring-shaped body (*ch.* in E, F).

many cases, perhaps in all cases, self-perpetuating by growth and division without loss of their identity, though their distribution to the daughter-cells often seems to be irregular. At a later period it was demonstrated that the centrioles or central bodies, which form the foci of mitotic cell-division, are likewise in many cases self-perpetuating

by a similar process, and are thus handed on in a perfectly definite manner from cell to cell during division. More recent cytological studies prominently raise the question whether still other formed bodies may not show a similar behavior. This question has not yet been definitely answered; but evidence has been coming in which places under suspicion the chondriosomes and the Golgi-bodies. Both these are in many cases handed on during division from mother-cell to daughter-cell, sometimes segregating with a precision that almost suggests that seen in case of the chromosomes. In many cases the chondriosomes take their place in separate groups about the equator of the karyokinetic spindle, draw apart into corresponding equal daughter-cells, move toward the poles, and enter the respective daughter-cells (Fig. 7). Whether these bodies individually considered have a permanent identity and are self-perpetuating by division is still a disputed question. Undoubtedly they are sometimes actually cut in two during cell-division; and in one well-determined case (spermatocytes of the scorpion *Centrurus*) all the chondriosomes become aggregated into a single ring-shaped body that is accurately divided in the course of two ensuing divisions (Figs. 8, 9).[11] Often, it is true, the chondriosomes seem to be passively sorted out or segregated without division into two approximately equal groups; but in all these cases the possibility remains open that they may multiply by division at an earlier period. Were such the case their history in division would be comparable to that often seen in case of the plastids of plant-cells; and in point of fact an important group of observers, headed by Meves and by Guilliermond,[12] have concluded from direct cytological observations that plastids may arise by the transformation of chondriosomes (Fig. 10). If this should prove to be correct, substantial

ground would be given for the conclusion that the chondriosomes may multiply by division, since the plastids undoubtedly have this power. Still less is known of the Golgi-bodies in this regard; but recent studies have clearly shown that these bodies, too, group themselves in a definite manner about the mitotic spindle during cell-

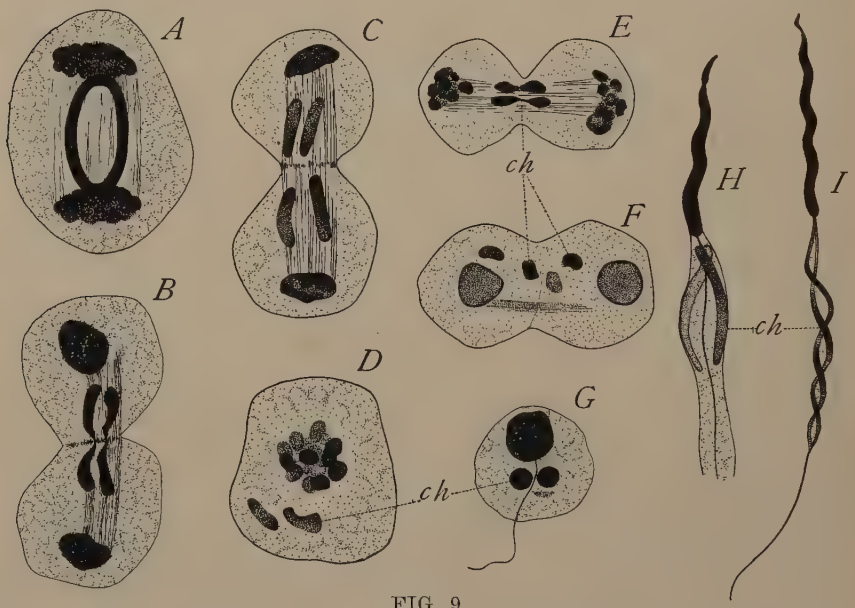

FIG. 9

Continuation of Fig. 8. Division of the chondriosome-ring into four parts, of which two pass to each daughter-cell (A-D), followed by the division of each of these in the ensuing cell-division (E, F).

division, and separate into two resulting daughter-groups (Fig. 11).

Doubtful or disputed points aside, it already seems clear, that in a large class of cases the specific substances of which the chondriosomes and Golgi-bodies are respectively composed are not formed *de novo* in the daughter-cells, but are somehow directly derived from corresponding components of the mother-cell. Recent researches

have also made it probable that, in some cases at least, their segregation in the daughter-cells can not be regarded as a merely passive or mechanical result of mitosis but is determined by a more definite and significant relation between these bodies and the centers of division; for as has recently been demonstrated by Bowen the chon-

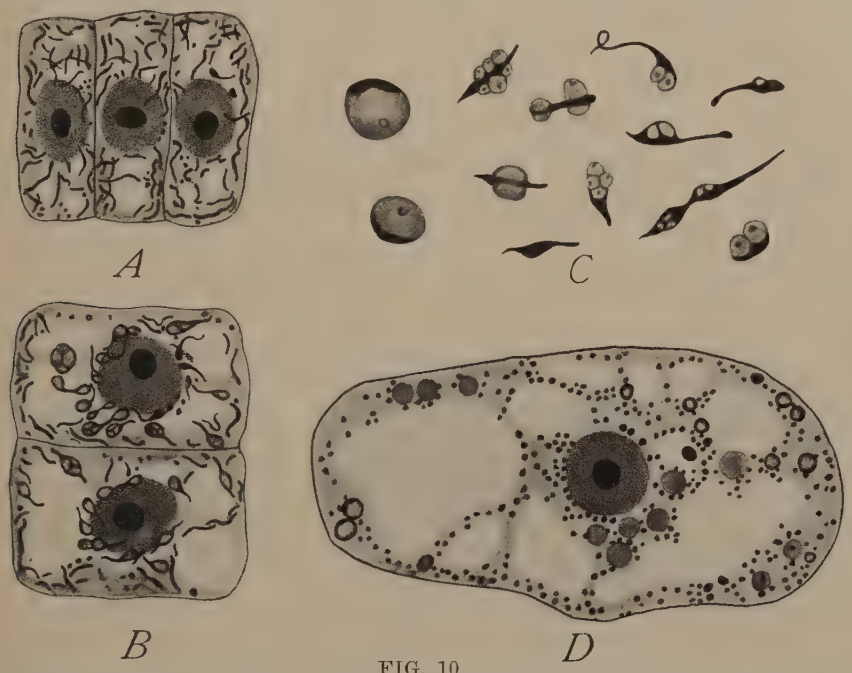

FIG. 10

Chondriosomes in the cells of plants, showing their supposed transformation into plastids (from GUILLIERMOND). A-C, from root-tips of barley; C, more enlarged amyloplasts or starch-formers; D, from potato-tuber, with mitochondria and leucoplasts.

driosomes are sometimes definitely oriented with respect to the centers in a manner that almost suggests that which characterizes the behavior of the chromosomes (Fig. 7). In all this we see surface indications of a more deeply lying process by which the complex cytoplasmic system may perpetuate itself intact from one generation to an-

other, or by a modification of this process may split up into secondary more limited systems according to a definite and predetermined plan. To this subject, so important for our conceptions of embryological development, we shall presently return; but this can better be appreciated after a broader survey of the origin of the cytoplasmic formed bodies in general, a problem which now opens before us with a new significance.

Laying aside all merely speculative attempts to solve this problem, we must admit that our actual knowledge concerning it is still in a very backward state. An important group of observers, led by Benda and Meves,[4] have urged the possibility that many of the formed bodies may arise by the transformation of chondriosomes, possibly also of Golgi-bodies, that are themselves transmitted by cell-division; but too much emphasis should not be laid on this view, which has met with much opposition and still remains of doubtful, or at best restricted, validity. It is still a widely prevalent belief that many of the formed bodies arise *de novo, i.e.,* that they are built up anew in the cytoplasm by localized processes of chemical and morphological synthesis; but in respect to this question we may readily fall into error. Permit me to illustrate this by reference to some old observations of mine on those classical objects for the study of protoplasm, the transparent eggs of certain sea-urchins and star-fishes.[13]

When mature these eggs show with great beauty a structure that has often compared to an emulsion, consisting of innumerable spheroidal bodies suspended in a clear continuous basis or hyaloplasm. These bodies are of two general orders of magnitude, namely, larger spheres or *macrosomes,* rather closely crowded and fairly uniform in size, and much smaller *microsomes* irregularly scattered between the macrosomes; and among the latter are

still smaller granules which graduate in size down to the limit of vision with any power we may employ. It is probable that both macrosomes and microsomes may be of several, perhaps many, different kinds; but this may here be disregarded (Fig. 12).

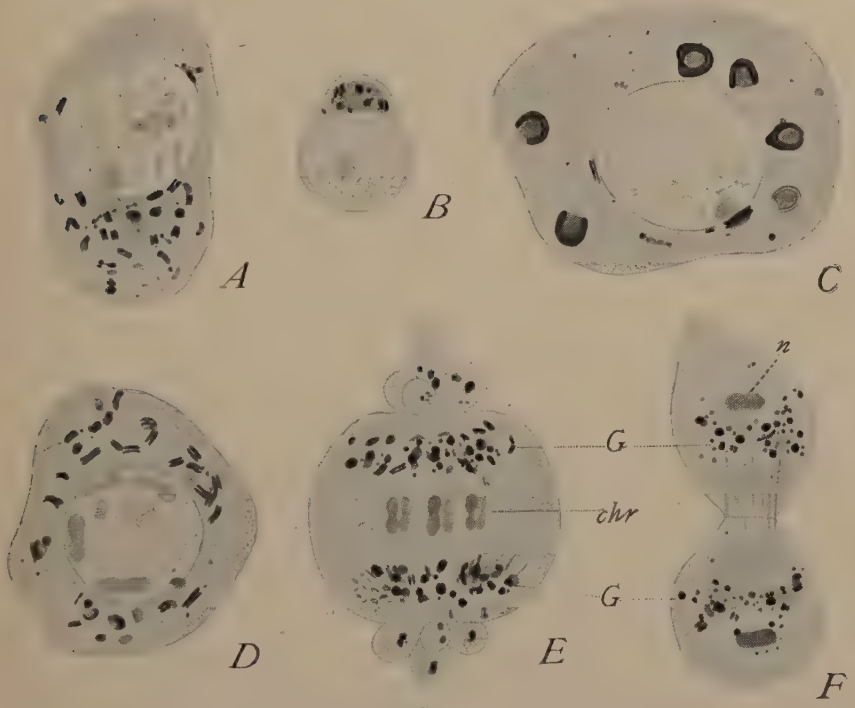

FIG. 11

Distribution of the Golgi-bodies in spermatocyte-divisions of Hemiptera (from BOWEN). In A and B, they are aggregated toward one pole; in C, larger and scattered; in D, fragmenting into "dictyosomes"; in E and F, passing to the poles. (*ch.*, the chromosomes, faintly stained; G, the Golgi-bodies.)

The important fact here to be emphasized is that this beautiful and regular structure is not a primary characteristic of this protoplasm. It is of secondary origin, arising by the appearance in the homogeneous ground-substance of extremely minute scattered bodies which by

growth and crowding together finally produce the emulsion-like structure. In the middle stages of this process the protoplasm gives an interesting picture (Fig. 13). When viewed under a relatively low magnification, *e.g.,* 300-500 diameters, only the larger bodies are seen; but as, step by step, we increase the magnification, step by step we see smaller and smaller bodies coming into view, at every stage graduating down to the limit of vision. This remains true even with the highest available powers. The microscopical picture offered by such protoplasm is thus somewhat like the telescopic picture of the sky. At each step in the improvement of the telescope new and fainter stars have come into view. At each step the astronomer has felt sure that still more powerful telescopes would bring into view stars hitherto unseen. The cytologist is equally sure that if the present limits of direct microscopical vision could be extended we should see dispersed bodies still more minute; and the invention of the ultramicroscope has in fact made us directly aware of the existence of suspended protoplasmic particles too small to be seen directly by the ordinary microscope, but made evident by their halos when viewed in powerful reflected light.

It is nearly certain that in these eggs some of the scattered bodies are derived as such from the mother-cell, in the form of pre-existing chondriosomes or Golgi-bodies. Aside from such bodies, however, there are many smaller ones that take origin in those most minute granules that lie near the limit of microscopical vision and seem to arise *de novo* in the hyaloplasm. But manifestly it is quite illogical to affirm an origin *de novo* of any formed body because it first becomes visible at a particular enlargement, even the greatest at our present command. Here, clearly, is an enormous gap in our knowledge. The

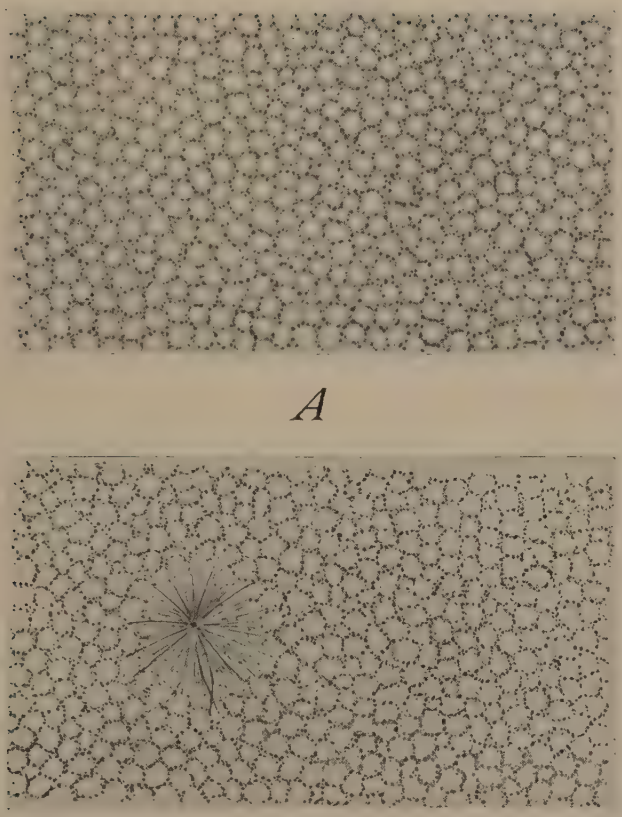

FIG. 12

Structure of protoplasm in the star-fish egg. A, from the living object; B, the same as it appears in sections. The star-like aster (sperm-aster) is connected with the fertilization of the egg.

resolving power of the microscope as limited by the wavelength of light ceases at a magnitude which in round numbers is not less than 200 submicrons, or somewhere in the neighborhood of $\frac{1}{125000}$ inch.[14] Such an order of magnitude seems to be far greater than that of the molecules of proteins and other inorganic substances. Estimates concerning the size of such molecules are perhaps not very safe, but it seems to be fairly well established that the molecule of such a protein as casein or haemoglobin is not more than about $\frac{1}{80}$ of the foregoing figure.[15] Even allowing for a large error, therefore, an immense gap remains between the smallest bodies visible with the microscope and the molecules of even the most complex organic substances. For these reasons alone, even had we not the evidence of the ultra-microscope, we should be certain that below the horizon of our present high-power microscopes there exists an invisible realm peopled by a multitude of suspended or dispersed particles, and one that is perhaps quite as complex as the visible region of the system with which the cytologist is directly occupied.

We have now arrived at a borderland, where the cytologist and the colloidal chemist are almost within hailing distance of each other—a region, it must be added, where both are treading on dangerous ground. Some of our friends seem disposed to think that the cytologist should halt at the artificial boundary set by the existing limits of microscopical vision and hand over his inquiry to the biochemist and biophysicist with a farewell greeting. The cytologist views the matter somewhat differently. Unless he is afflicted with complete paralysis of his cerebral protoplasm he can not stop at the artificial boundary set up by the existing limits of microscopical vision. He is rudely pushed forward by the impact of a series of stubborn facts with which he must somehow try to reckon. He can

not get out of his head the microscopical picture of progressively diminishing magnitudes which, as if viewed through an inverted telescope, disappear at last in vanishing perspective in the sub-microscopical depths. At the nearer end of the picture are the plastids, larger or smaller, and self-perpetuating by growth and division. A step beyond are the central bodies, often of such minute-

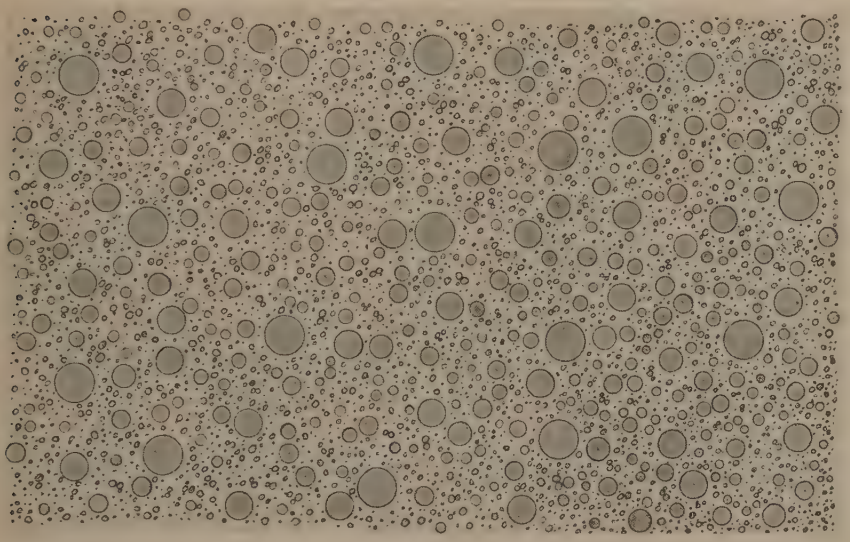

FIG. 13

Protoplasm from the growing star-fish egg, slightly schematized, showing the formation and growth of formed bodies (macrosomes and microsomes).

ness as to lie almost on the horizon of microscopical vision, but still capable of self-perpetuation by growth and division, of enlargement to form much larger bodies, and of exerting far-reaching effects on the surrounding structures. One more step, and the cytologist is beyond the help of the microscope, wandering blindly in an unseen but none the less real world. The pathologists tantalize him with visions of disease-germs which no eye has yet

seen, so minute as to pass through a fine filter, yet beyond a doubt self-perpetuating and of specific type. The geneticists continually crowd upon him with fresh demonstrations of those unseen somethings, aligned in orderly array in the nuclear threads, each preserving its own specific type amid all the shifting events of the nuclear life, without modification by its fellows, and somehow, generation after generation, handing on its individual characteristics to its descendants.

With all this in mind the cytologist finds reason enough to exercise his wits upon the apparently structureless ground-substance or hyaloplasm that seems to constitute the fundamental basis of protoplasm and to be the source of many of its formed elements. He can not resist the evidence that the appearance of a simple, homogeneous colloidal substance that is offered by the hyaloplasm is deceptive; that it is in reality a complex, heterogeneous or polyphasic system. He finds it difficult to escape the conclusion, therefore, that the visible and the invisible components of the protoplasmic system differ only in their size and degree of dispersion; that they belong to a single, continuous series; and that the visible structure of protoplasm may thus give us something like a rough magnified picture of the invisible. If so much be granted, the cytologist is led on to the conclusion that the ultra-microscopical dispersed particles of the hyaloplasm may be as highly diversified chemically as are the visible formed bodies; that they may be of all orders of magnitude; and that it is they which constitute the sources, or at least the formative foci, of those larger formed bodies that we have so often, but erroneously, assumed to arise *de novo*. For my part, I am disposed to take a final step by accepting the probability that many of these particles (I do not say all) as if they were ultra-microscopical plastids, may have a

persistent identity, perpetuating themselves by growth and multiplication without loss of their specific individual type. These possibilities, long since urged by speculative writers, have in recent years been treated as almost negligible; but sooner or later, I think, they will call for more serious consideration, particularly in view of the results of embryological investigation, presently to be considered.

Among these possibilities the one least likely to meet with approval is that some, and possible many, of the sub-microscopical components may be self-perpetuating. Good biological society long since placed its ban on mediaeval notions of this type and turned a cold shoulder upon all corpuscular or micromeritic conceptions of the cell-substance. Seriously to consider anything approaching to them requires at this day a certain amount of courage. By some singular process of casuistry such conceptions have been supposed to place the fundamental problems of biology beyond the reach of scientific investigation. An ingenious philosopher has said that corpuscular hytheses in general would make of the world—or of the cell—a mere puzzle-picture which we cut up into small pieces only to put them together again to form the same picture. In spite of this, however, physical science pursues its task of cutting the world up into smaller and smaller pieces and has thus far seemed to manage fairly well with the pictures rebuilt from them. Similar in principle was the procedure of the fathers of the cell-theory when they resolved the living body into its component cells. Some of the successors of those pioneers, even down to our own day, have seemed to find something very reprehensible in this operation; nevertheless the cell-theory still seems to survive as an effective means of biological progress. Perhaps therefore the youthful sciences of cytology and genetics

may hope for lenient treatment if they try to go somewhat further along the path marked out by their forefathers. Many earlier hypotheses of this type failed because too much was claimed for them, either by their authors or by critics who wished to destroy them. Such was the case, for instance, with Weismann's speculations on biophores and the architecture of the germ-plasm; with those of Darwin and De Vries on gemmules and pangens; and those of Altmann on bioblasts and the general significance of the protoplasmic granules. But we are not here concerned with merely theoretical or *a priori* constructions but with questions of fact that are forced on our attention by concrete microscopical and experimental studies on the cell. It is our business as students of cytology and genetics to answer these questions if we can. And lastly I would remark that I am not here attempting to resuscitate the old conception of the cell as an assemblage or colony of elementary organisms or primary vital units—perhaps it is such, perhaps not—nor am I able to see how the possibilities here considered are in any manner out of harmony with the conception of the cell as a colloidal system.

II

We have, as it were (to return to Bergson's metaphor), taken the cell to pieces. How shall we put it together again? In this second stage of our inquiry we first come to closer quarters with the problem of the physical basis of life and encounter the unsolved riddle. We try to disguise our ignorance in regard to it with learned phrases. We are forever conjuring with the word "organization" as a name for that which constitutes the integrating and unifying principle in vital processes; but which one of

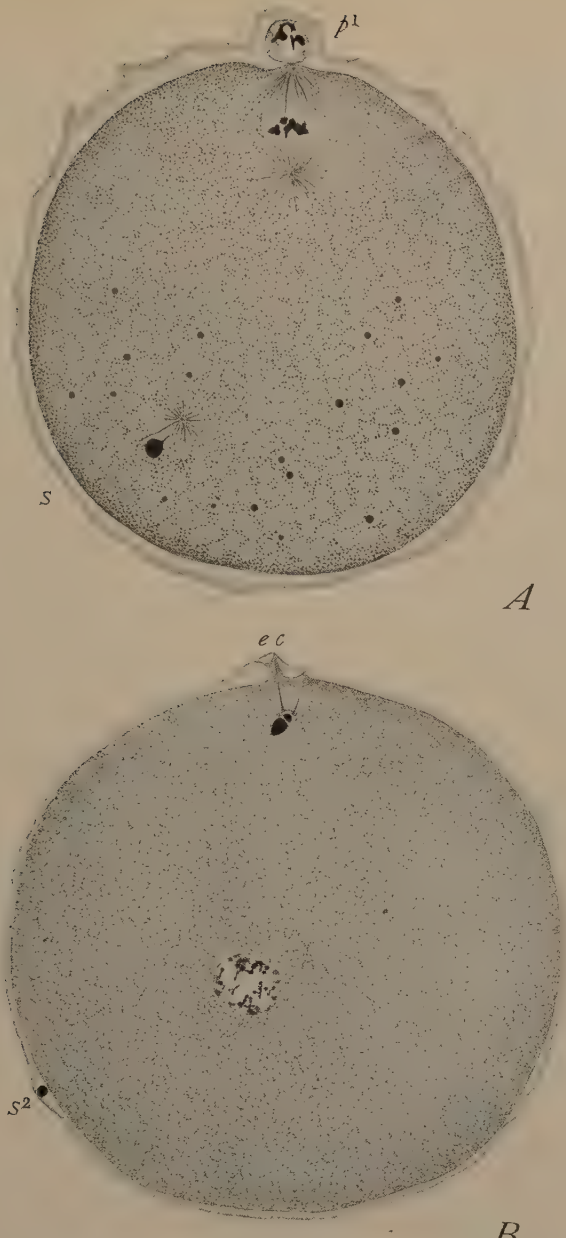

FIG. 14

The eggs of a worm *Thalassema* (A) and of a sea-urchin *Toxopneustes* (B) at the time of fertilization. In A the sperm is seen near *s*, while near *p* the formation of the polar bodies is in progress. In B, the sperm is seen above, near *e.c.*, about three minutes after its penetration into the egg, and the egg-nucleus below.

us is able to translate this into intelligible language? We say pedantically—and no doubt correctly—that the orderly operation of the cell results from a dynamic equilibrium in a polyphasic colloidal system (p. 8). In our mechanistic treatment of the problem we commonly assume this equilibrium to be somehow traceable to an original pattern or configuration of material particles in the system, as is the case with a machine. Most certainly conceptions of this type have given us an indispensable working method—the method which almost alone is responsible for the progress of modern biology—but the plain fact remains that there are still some of the most striking phenomena of life of which it has thus far failed to give us more than the most rudimentary understanding. Foremost among these stand the phenomena of development, which more than any others bring home to us the nebulous state in which the whole concept of organization still remains. When the organism has come to full development it consists of co-ordinated parts, which display a multitude of cunning devices—anatomical, physiological or chemical—that make provision for the harmonious co-operation of its activities for its protection and maintenance. To this extent its organization is obvious and intelligible; and to the same extent the organism is clearly a piece of mechanism, a living machine. But let us review the building of this machine by following it backward, step by step, to its starting point. Step by step we find the intricate machinery of life vanishing before our eyes until nothing remains but a single cell, the egg (Fig. 14). In this cell, complex though it may be in its own way, not a trace seems to remain of the co-ordinating and unifying devices of the adult; but who will maintain that the egg is not as specifically organized and as truly alive as the adult to which it gives rise?

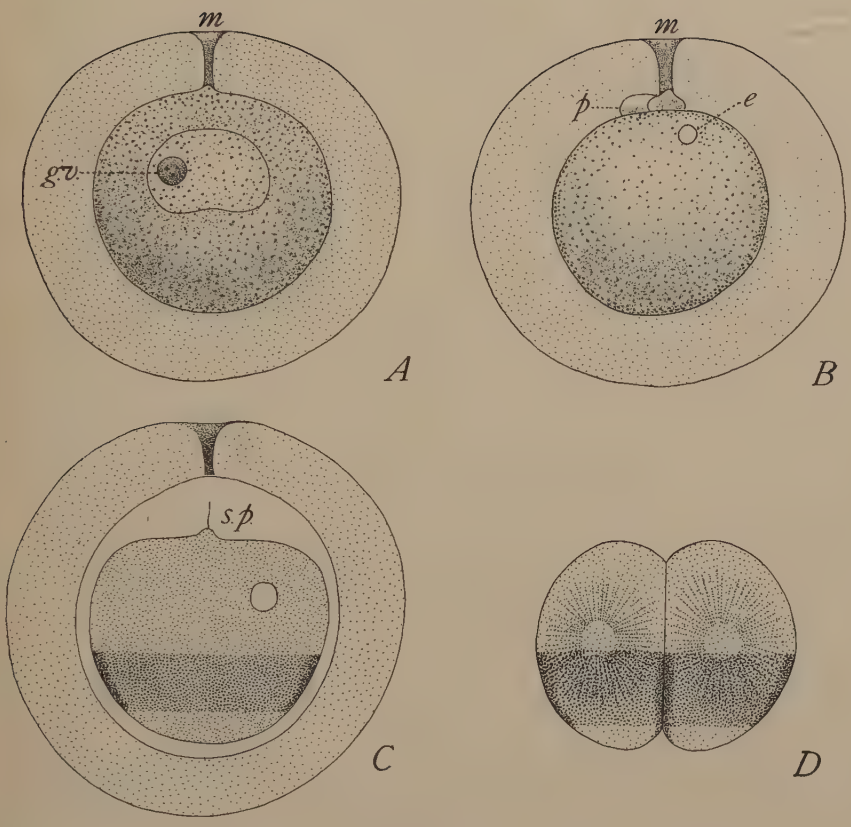

FIG. 15

A, egg of the sea-urchin, *Paracentrotus lividus* (from Boveri), before its maturation of fertilization, uniformly pigmented; B, the same just after formation of the polar bodies (*p.*); C, the same slightly later (in this case just after entrance of the sperm at s.p.) when ready for fertilization, with pigment localized in a sub-equatorial belt; D, the 2-cell stage.

It was a strange notion of the seventeenth century that the embryo exists from the beginning, preformed in the egg, and has only to unfold itself during development; and out of this phantasy grew one of the most singular controversies in the history of modern science. It was halted in the middle of the eighteenth century by the observations of Caspar Friederich Wolff, who decisively overthrew the doctrine of preformation in its original form. Modern research, nevertheless, has dressed this notion out with a new disguise in the conception of prelocalization in the egg. The embryo, it is said, is already present in the egg, not indeed in its completed form but as it were blocked out "in the rough" in the cytoplasm, so that development has only to impress upon it the finishing touches. This conception grew out of certain well determined facts, to the establishment of which experimental embryology, cytology and genetics all contributed. Prominent among them is the fact, demonstrated by studies on certain hybrids, that certain general features in the early development seem to be determined by the cytoplasm (oöplasm) of the egg alone, uninfluenced for a time by the sperm.

In harmony with this, up to a certain point, are the following facts. Both observation and experiment have conclusively proved that during the cleavage of the egg its substance undergoes a definite differential distribution to the embryonic cells, being parceled out, as it were, in such manner that each cell receives a particular allotment of specific materials by which its immediate development is determined or conditioned. The pattern of cleavage, thus represents a kind of mosaic-work of such materials localized within the boundaries of its component cells. It was at first assumed by Roux and by Weismann that the determining materials thus segregated

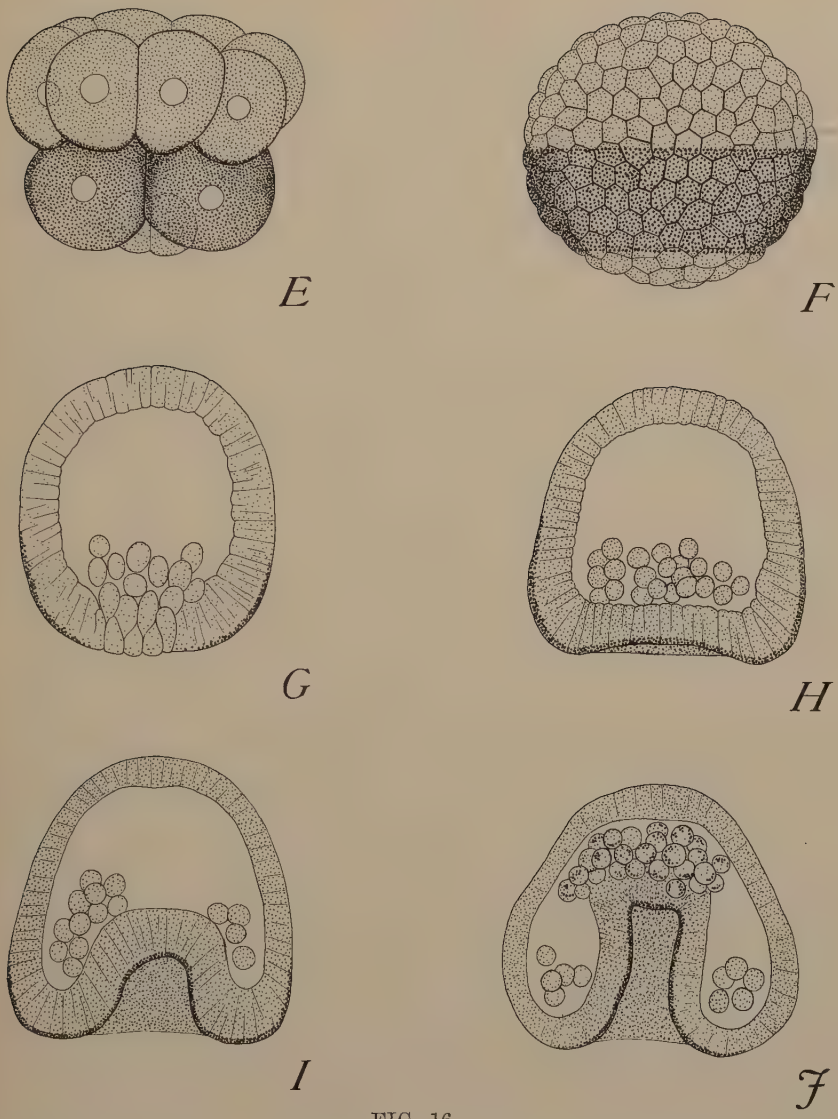

FIG. 16

Continuation of Fig. 15. Later stages of the sea-urchin *Paracentrotus* (from BOVERI) showing fate of the three original zones. E, 16-cell stage; F, blastula; G, inwandering of mesenchyme-cell from the lower clear zone; H, beginning of gastrulation; I, J, invagination of pigmented zone to form the archenteron.

were contained in the nucleus and that the cytoplasm or oöplasm is indifferent in character. This conception was overthrown by experiments which demonstrated that by subjecting the egg to pressure during cleavage the relative positions of the nuclei might be widely altered without materially affecting the cytoplasmic materials; yet such eggs, when released from pressure, often produce nearly or quite normal embryos.[16] It must therefore be cytoplasmic materials, rather than nuclear, that undergo a differential distribution by cleavage—a result supported by numerous cytological observations which have shown that the cytoplasmic components of different cells often show characteristic differences made visible by the presence of pigment, of specific types of granulation, or other characters.

The conception of an original germinal prelocalization in the cytoplasm seems at first sight to be supported by the fact that these different oöplasmic materials are often visible as such in the egg before cleavage begins, often before it is fertilized; and especially by the fact that even at this time they sometimes display a definite structural pattern which in certain important respects already offers a plan or outline of the coming embryo. The germ-forming regions or oöplasmic areas thus indicated are not marked off by sharply defined or fixed boundaries prior to cleavage, but as this process proceeds they become clearly defined by cleavage-planes which isolate their materials in particular cells, or groups of cells, of the early embryo. A well-known example of these facts is offered by the sea-urchin *Paracentrotus lividus* in which, as demonstrated by Boveri, the egg *at a certain period* prior to its fertilization shows three horizontal zones (Fig. 15, 16), an upper clear one which produces the ectoderm of the larva, a middle red-pigmented one that gives rise to the entoderm

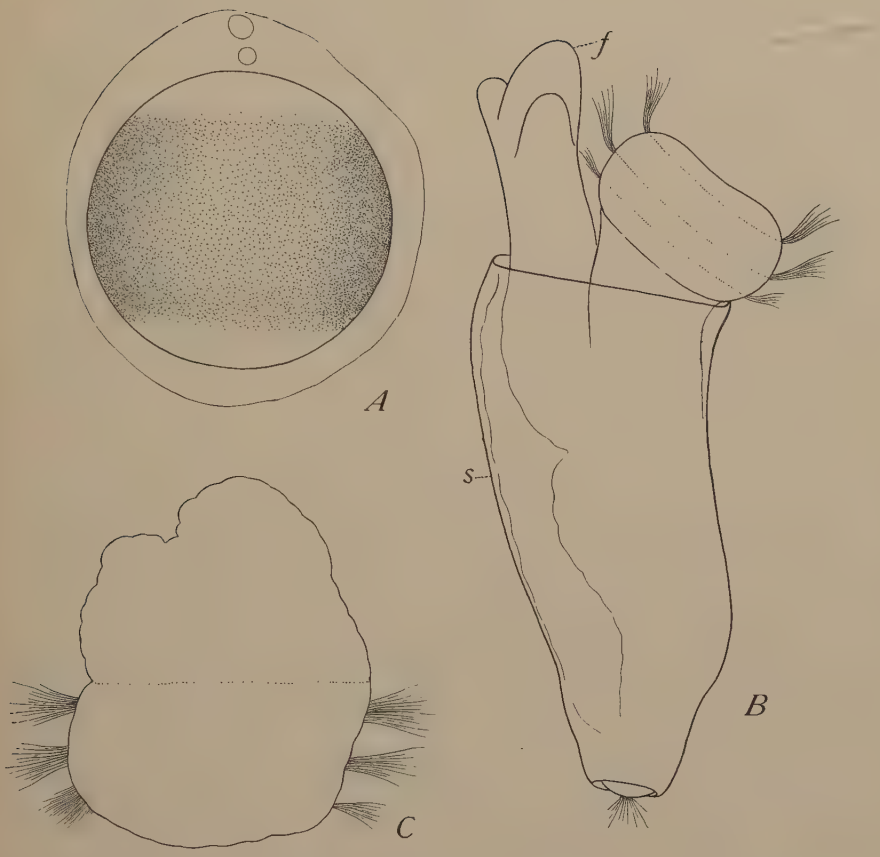

FIG. 17

Egg and larvae of the mollusk *Dentalium*. A is the egg just after fertilization, showing a broad equatorial pigment zone and two white polar areas. B, normal larva of 72 hours. C, active larva of the same age, from an egg from which the lower polar area had been cut away, lacking the foot, shell and other important structures.

and a smaller lower clear zone which produces the larval mesenchyme. In the mollusk *Dentalium* the egg likewise shows three zones which have a similar (though not precisely identical) relation to the formation of the larval body. Experimental operations on the egg have proved that these areas or "germ-forming regions" have a definite specification or predetermination which can be altered only in minor degree by experimental methods. In the sea-urchin, for example, fertilized fragments of the egg do not gastrulate unless at least a portion of the red zone be present; and in *Dentalium* removal of the lower white area causes not merely the production of a smaller larva but one that shows very definite and *constant* structural defects (Fig. 17). In the ascidian *Styela partita* the egg, before cleavage begins, shows a still more specific prelocalization, the oöplasmic pattern already showing very clearly bilateral symmetry and antero-posterior differentiation, and in some degree a prelocalization of the materials for not less than five important structures of the future larva (Fig. 18).[16, 17]

All this, evidently, demonstrates the fact of germinal prelocalization and on its face seems to sustain the theory of the embryo in the rough; but a more critical examination dispels this latter impression. For observation and experiment alike indicate that prelocalization in the oöplasm is a secondary product of an earlier development in the egg; the rough model, in other words, is blocked out in the oöplasm by an epigenetic process. In Boveri's sea-urchins, the horizontal zones do not appear—and, so far as we can determine, do not exist—before the polar bodies have been extruded from the egg. Only after they have been formed does the red-pigmented cortical oöplasm, at first extending around the whole periphery of the egg, stream toward the equator to form the entoderm-form-

ing zone (Fig. 15). In the ascidian, too, the striking visible pattern seen at the beginning of cleavage does not at first exist but is swiftly built under the eye of the observer by streaming movements of the oöplasm that take place immediately upon entrance of the sperm into the egg (Fig. 17). In cases like these, where the localizing opera-

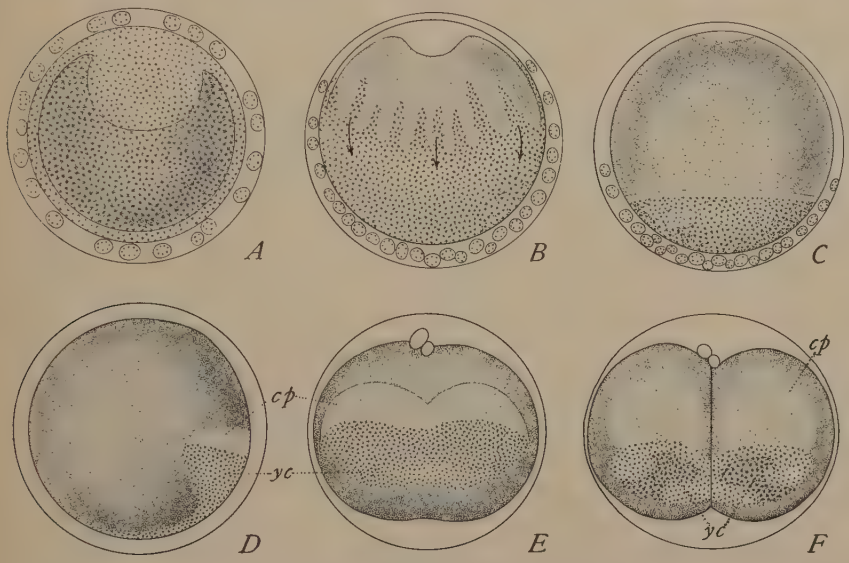

FIG. 18

Localizing activities in the eggs of an ascidian *Cynthia*, showing early localization of the regions of the future embryo, as indicated by differently shaded areas (from CONKLIN). The bilaterality of the future embryo is clearly indicated in D (side view) and E (rear view); and the first cleavage-plane in F marks exactly the median plane.

tions may readily be followed by the eye, the egg offers an impressive spectacle when busily engaged at its work of blocking out the embryo, without visible tools or model, but with an uncanny air of deliberate purpose and mastery of technique that any human artist might envy.

Beyond a doubt the movements and regroupings of material which give rise to the visible pattern are expres-

sions of an underlying more fundamental organization that escapes the eye; but it is precisely this organization of which we are ignorant. Experiment has shown in one case at least (the eggs of nemertines) that fragments from eggs taken prior to the period of visible localization develop as miniature wholes,—a fact which points unmistakably to the conclusion that the fundamental pattern of localization has not yet been established in the oöplasm at that time. It has thus been made probable that even the most general features of the organism, perhaps even such fundamental ones as polarity and bilaterality, are not present at the beginning but like other characters are established in the egg by a process of epigenesis.[18]

The point of especial interest to the cytologist is the fact that the visible patterns in the oöplasm produced by configurations of the various formed bodies do not constitute its fundamental organization but are only an outward sign or index of that organization. For in the first place (as has just been shown), these patterns are absent in the earliest stages, being produced subsequently by processes of development. In the second place, as demonstrated by the experiments of Lyon, Morgan, Lillie, Conklin and others, the visible patterns may in many cases be disturbed or even almost obliterated by subjecting the egg to a strong centrifugal force (by which the formed bodies are displaced) without destroying the capacity for later normal development, and often without even serious temporary impairment. Once more, therefore, we are driven to the conclusion that *the primary basis of the egg-organization lies in the ground-substance or hyaloplasm;* and that it is primarily the components of this system that are sifted apart and distributed during the cleavage of the egg according to a perfectly definite order. The visible

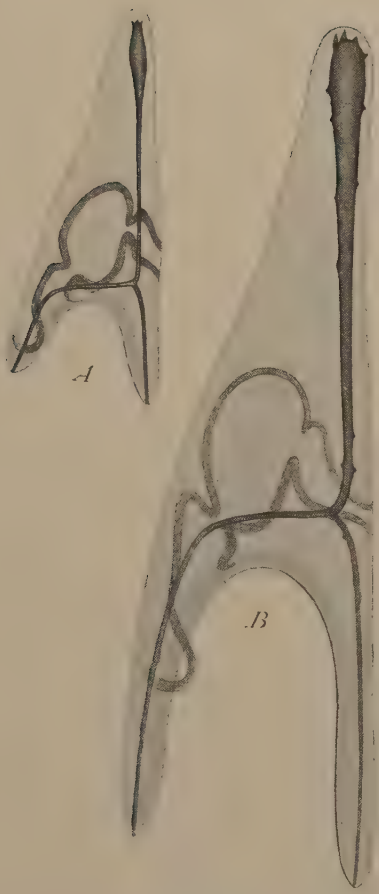

FIG. 19

Normal sea-urchin larva (*Echinus*) from a whole egg (B), and a dwarf merogonic larva (A) from a fertilized egg-fragment (BOVERI).

formed components follow this order; they do not create it.[19]

What then constitutes the fundamental or primary organization of the egg? No one is yet able to answer. The embryologist, the cytologist, the physiologist and the biochemist—all alike have thus far only skirted the outermost rim of the problem. We can not predict how far the cytologist of the future may be able to penetrate within it; but it would seem that sooner or later his way will finally be blocked by inherent limitations of the microscope determined by the wave-length of light. If we are ever to find our way into the innermost arcanum of the cell all the resources not only of cytology but also of experimental embryology, genetics, biophysics and biochemistry must be marshaled. The problem of organization has as yet barely been touched by purely physicochemical analysis. Genetics, it is true, has of late made remarkable advances toward the study of the nuclear organization but leaves unsolved the problem of the "organism as a whole." Experimental embryology has elucidated the phenomena of development by many important discoveries,[20] but at the same time has emphasized our failure thus far to solve the central problem—it was indeed from this source, that Driesch, a distinguished pioneer in this field, drew the facts on which he based his famous argument against the machine-theory of development and attempted to set up in its place a new philosophy of vitalism. This argument was originally based on his own remarkable discovery that a single cell (blastomere) isolated from its fellows at the 2-cell or 4-cell stage of development, is able to produce a perfect dwarf larva that is a precise miniature of the normal one from a complete egg. The argument was re-enforced by the demonstration nearly at the same time, by the brothers Hertwig

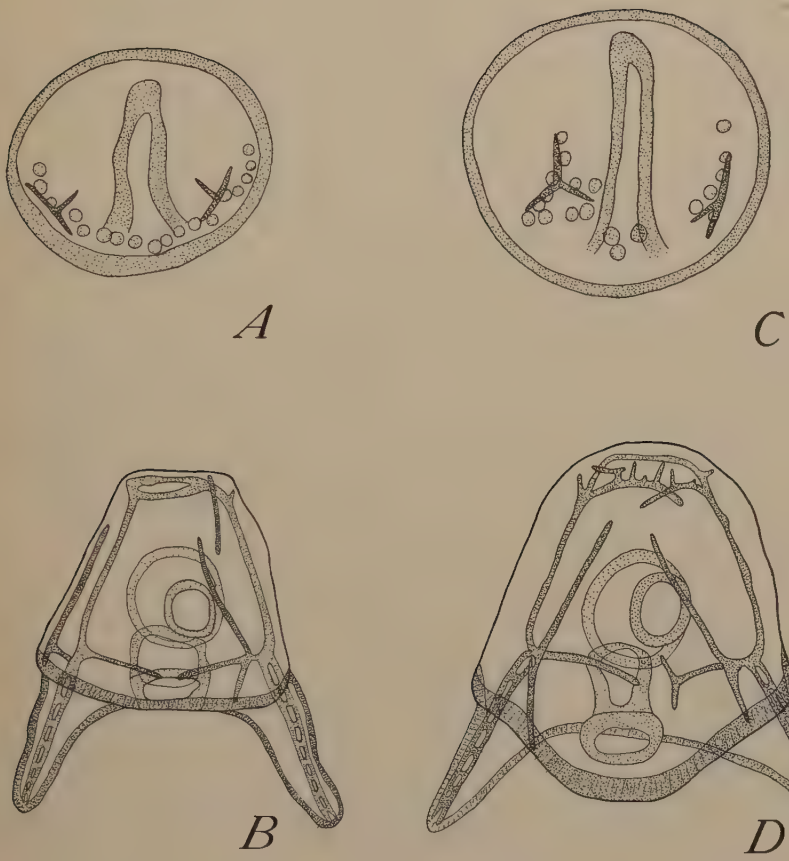

FIG. 20

A, B, Normal larvae earlier and later, each from a single egg of *Sphaerechinus*. C, D, corresponding stages of giant larvae from double eggs (BIERENS DE HAAN).

and by Boveri, that a non-nucleated *fragment* of an unfertilized egg, may be fertilized by a sperm ("merogony") and may develop into a perfectly formed dwarf larva closely similar to that derived from an isolated blastomere (Fig. 19).[21] Even more astonishing was the converse discovery by Driesch and zur Strassen that one larva, normally formed but of double the normal size, may arise from two eggs fused to form one "giant" egg (Fig. 20).[22]

To the developing organism, it would seem to be all one whether it builds with one egg, two eggs, or a piece of an egg. How shall we deal with these facts under the mechanistic assumption of an original fixed structural pattern in the egg? Or, if we prefer the other horn of the dilemma, granting that the egg can at will make over the original pattern so as to fit a new emergency, what kind of original configuration in the germ makes possible such an operation and determines its character?

Difficulties of this type, according to Driesch's argument, constitute the rock on which the whole mechanistic interpretation of organization and development splits.[23] The argument may fail to convince us—it does fail; but it still remains without adequate answer if it be not unanswerable. All, on the contrary, now points to the essential correctness of Driesch's contention that at the real beginning of development the cytoplasm of the egg is devoid of any structural pattern or machine-like configuration that foreshadows the plan of the future embryo. Not alone the structural details of the embryo but the very plan on which it is built is constructed anew in the course of development. May we then seek a solution of the puzzle in the nucleus of the egg, in the hope of finding here the primary determining causes of the organization of the egg considered as a whole? Perhaps. Whether the nucleus

represents the sole, or even the primary, physical basis of heredity, as maintained by some investigators, is still an open question; but as has earlier been indicated it seems no longer open to doubt that the development of particular characters somehow depends upon the presence in the nucleus of corresponding particular and separate hereditary units; and the conclusion loses nothing of its force by reason of the fact that the precise nature of these units is still unknown. We know from the celebrated experiments of Boveri and his successors that normal development depends on the normal combination of these units.[24] Conversely, genetic evidence is now opening far-reaching horizons of future discovery by the accumulating demonstration that no one of the nuclear units plays an exclusive rôle in the determination of any single character. It has been proved that the individual unit often affects the production not merely of one character but of many. The converse probability is shaping itself that the production of any single character requires the co-operation of several or many units, possibly of all. I believe it is not a great overstatement when I say that every unit may affect the whole organism, and that all the units may affect each character. We begin to see more clearly that the whole cell-system may be involved in the production of every character. How, then, are hereditary traits woven together in a typical order of space and time? It is the same old puzzle, made larger and more insistent, but not yet, so far as I can see, brought nearer to its solution. We are ready with the time-honored replies: It is an act of the "organism as a whole"; it is a "property of the system as such"; it is "organization." These words, like those of Goldsmith's country parson, are

"Of learned length and thundering sound."

Once more, in the plain speech of everyday life, their meaning is: *We do not know.*

I do not in the least mean by this that our faith in mechanistic methods and conceptions is shaken. It is by following precisely these methods and conceptions that observation and experiment are every day enlarging our knowledge of colloidal systems, lifeless and living. Who will set a limit to their future progress? But I am not speaking of tomorrow but of today; and the mechanist should not deceive himself in regard to the magnitude of the task that still lies before him. Perhaps, indeed, a day may come (and here I use the words of Professor Troland)[25] when we may be able "to show how in accordance with recognized principles of physics a complex of specific, autocatalytic, colloidal particles in the germ-cell can engineer the construction of a vertebrate organism"; but assuredly that day is not yet within sight of our most powerful telescopes. Shall we then join hands with the neo-vitalists in referring the unifying and regulatory principle to the operation of an unknown power, a directive force, an archaeus, an entelechy, or a soul? Yes, if we are ready to abandon the problem and have done with it once for all. No, a thousand times, if we hope really to advance our understanding of the living organism. To say *ignoramus* does not mean that we must also say *ignorabimus*. I do not believe that a confession of ignorance leaves us with no resource save vitalism. To maintain that observation and experiment will not bring us nearer to a solution of the puzzle would be to lapse into the dark ages. Perhaps Professor Henderson is right when he expresses his belief that organization has finally become a category that stands beside those of matter and energy.[26] Perhaps there is no problem, or none that we can formulate without talking nonsense. Perhaps we should go no further

than to record and analyze the existing order of phenomena in living systems, without losing sleep over the imaginary problem of a unifying principle. Let us politely salute all these uncomfortable possibilities and go our way. For my part, I find it more amusing to look forward to a day when the great riddle may give up its secret.

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